

21. (Withdrawn) A computer system, intended to generate structures and/or perform rational drug design for the 30S ribosome or complexes of the 30S ribosome with a potential modulator, the system containing either (a) atomic coordinate data according to a table selected from the group of tables 1 to 4, said data defining the three-dimensional structure of 30S or at least one sub-domain thereof, or (b) structure factor data for 30S, said structure factor data being derivable from the atomic coordinate data of a table selected from the group of tables 1 to 4.

22. (Withdrawn) A computer readable media, with either (a) atomic coordinate data according to a table selected from the group of tables 1 to 4 recorded thereon, said data defining the three-dimensional structure of 30S ribosome, or at least one atom or at least one sub-domain thereof, or (b) structure factor data for 30S ribosome recorded thereon, the structure factor data being derivable from the atomic coordinate data of a table selected from the group of tables 1 to 4.

### **REMARKS**

Claims 1-22 are currently pending in the application. Claims 14-22 have been withdrawn by the Examiner as being drawn to a non-elected group. Claims 5-11 have been withdrawn by the Examiner as being drawn to the non elected species. Claims 1-4, 12 and 13 are examined on the merits.

Claims 1-13 are currently amended. The amendments find support in the specification and are discussed in the relevant sections below. No new matter is added.

### ***Species Election***

The Office action states in paragraph 3 that “Claims 5-11 have been withdrawn due to being directed to species other than the elected species, an antibiotic which is paromomycin”. However, Applicant notes that claim 7 recites “A crystal of a 30S subunit bound to the antibiotic paromomycin having a tetragonal space group  $P4_12_12$  with unit cell dimensions of  $a = 401.4 \text{ \AA}$ ,  $b = 401.4 \text{ \AA}$ ,  $c = 175.9 \text{ \AA}$ ”. Since claim 7 is directed to the elected species of an antibiotic, paromomycin, Applicant contends that claim 7 should not have been withdrawn from

consideration by the Examiner, and should have been examined on the merits. Accordingly, Applicant requests an examination of claim 7 in a non-final office action.

As discussed further below, Applicant has amended claims 1-13 to more clearly define Applicant's invention. In view of said amendments and in view of the arguments presented below, Applicant contends that the examined claims 1-4, 12 and 13 are in condition for allowance. Accordingly, Applicant respectfully requests examination of claims 5-11, which are directed to the instant invention encompassing nonelected antibiotic species.

### ***Priority***

The Examiner acknowledges Applicant's claim for foreign priority based on applications filed in the United Kingdom, but states that the certified foreign priority documents are not in the application and suggests that the Applicant resubmit the priority documents for consideration.

Applicant notes that certified copies of all six foreign priority documents were filed January 16, 2002, and received by the USPTO as indicated by the return receipt postcard. Applicant also notes that on November 6, 2003, certified copies of two of said priority documents (United Kingdom 0017376.5, filed 7/14/2000, and United Kingdom 0022943.5, filed 9/19/2000) were submitted with US application 09/904,779. Applicant respectfully requests that the Examiner consider UK0017376.5 and UK0022943.5, submitted with US application 09/904,779. Applicant is in the process of obtaining the remaining four priority documents and will forward them to the Examiner upon their receipt by Applicant.

### ***Objections***

The title of the instant application is objected to by the Office Action because it is alleged that the title is not descriptive. As suggested by the examiner, the instant title has been changed to "Crystal structure of the 30S ribosome." Removal of the objection is respectfully requested.

### ***Claim Rejections- 35 USC 112, Second Paragraph***

Claims 1 and 12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as his invention.

The Office Action asserts that Claim 1 is indefinite because the recitation of the phrase “..crystal of a 30S subunit bound to an antibiotic Z...” encompasses non-elected species of antibiotics. Specifically the office action states that “the table has species beyond the elected species, paromomycin, which causes the claim to be vague and indefinite. Streptomycin, spectinomycin, tetracycline, pactamycin, and hygromycin B are non elected species; therefore, it is unclear to which specie the claimed invention is directed. Further, it is unclear what is controlling the metes and bounds of the claimed invention. Clarification of the metes and bounds is required.”

Accordingly, Applicant traverses the rejection of Claim 1 on the grounds that the table has species beyond the elected species, paromomycin, which causes the claim to be vague and indefinite because the five non-elected antibiotic species are clearly recited in Claim 1. Applicant contends that Claim 1, as amended, is in condition for allowance in view of said amendment and in view of the arguments presented below, and respectfully requests examination of Claim 1 with respect to the nonelected antibiotic species recited in claim 1.

The Office Action further requires clarification of the metes and bounds of the claimed invention. Applicant hereby clarifies that the metes and bounds of the invention encompassed by Claim 1 is a crystal of a 30S ribosomal subunit bound to one of the 6 recited antibiotics, which consists of a tetragonal space group as specified in the Table recited in claim 1. In view of the clarification of the metes and bounds of the invention, Applicant contends that claim 1 is not vague and indefinite. Therefore, Applicant respectfully requests reconsideration and withdrawal of this rejection.

Claim 12 is also rejected under 35 U.S.C. 112, second paragraph, as being indefinite. The Office Action asserts that the recitation of the phrase “better( numerically less)” is indefinite because it is not clear what comparison the limitation “better” refers to. While not acquiescing to the rejection, and in order to more clearly define the claimed invention, Applicants have amended the claims to delete the word “better”.

Accordingly, Claim 12 has been amended to recite “A crystal of a 30S ribosomal subunit bound to the antibiotic selected from the group paromomycin, streptomycin, spectinomycin, tetracycline, pactamycin and hygromycin B, having a resolution numerically less than about 3 Å”. Support for the structure of amended claim 12 is provided at page 4, lines 21-28 and page 5, lines 1-4, wherein it is stated, “ In a first aspect, the present invention provides a crystal of the *Thermus thermophilus* 30S subunit bound to an antibiotic Z (where Z is defined below), having a tetragonal space group P4<sub>1</sub>2<sub>1</sub>2 with unit cell dimensions of about:

Z	a(Angstroms)	b(Angstroms)	c(Angstroms)
Paromomycin	401.375	401.375	175.887
Paromomycin	401.2	401.2	176.4
Streptomycin	401.375	401.475	175.887
Streptomycin	401.375	401.375	175.887
Tetracycline	401.158	401.158	176.994
Pactamycin	401.719	401.719	177.002
Hygromycin B	402.063	402.063	175.263

An advantageous feature of the structure is that it diffracts beyond 3Å resolution.” In view of this amendment to Claim 12, Applicant submits that this rejection has been overcome.

***Claim Rejections-35 USC § 112, First Paragraph***

***Enablement***

Claims 1-4, 12, and 13 are rejected under 35 U.S.C. 112, first paragraph, enablement, because the office action asserts that “the specification, while being enabling for a crystal

structure of the *Thermus thermophilus* 30S subunit having a resolution of 3.05 Å, which have atom coordinates instantly disclosed, does not reasonably provide enablement for any 30S subunit, or any 30S subunit having a resolution numerically less than about 3 Å”.

The Office Action further states that “claims 1-4 and 13 contain the open claim language word “having” in line 1 of each claim, thus, including crystals, which contain more structure than the unit cell dimensions as defined in Tables 1-4”.

Applicants submit that claims 1-4 and 12-13 are properly enabled for a crystal structure of a 30S ribosomal subunit derived from *Thermus thermophilus*, as well as from other prokaryotes. As of the earliest priority date of the instant application it was known that there was a high degree of conservation in the 30S structure (see Fujita et al., 1998; 9:3-12, Genome Inform. Ser. Workshop Genome Inform.; Altamra et al., 1991, J. Biol. Chem., 266:6195-6200; Moazed et al., 1987, Nature, 327:389-394; Lake et al., 1982, Proc. Natl. Acad. Sci. USA, 79:5948-5952; Woese et al., 1977, Proc. Natl. Acad. Sci. USA 74:5088-5090)..

The specification states at page 3, lines 18-20, [t]he 30S ribosomal subunit is a major target for antibiotics. The ribosome is a useful target for antibiotics since the **structure of the 30S is widely conserved between prokaryotes**, allowing for broad spectrum antibiotics. (emphasis added)”

The specification also states at page 11, lines 10-,

“This methodology provides those of skill in the art a means to provide 30S crystals of *T.thermophilus*. **The conservation of ribosome structure, particularly regions of structure essential for function, between prokaryotes, for example prokaryotes which are human pathogens, such as *Staphylococcus spp*, and the like, allows the structure herein to be useful in the provision of anti-bacterial agents in general.** Thus, the structure may be used to solve 30S subunits by the technique of molecular replacement. In such a method, x-ray diffraction data are obtained from crystals of a 30S subunit from another species, e.g. a species of a bacteria pathogenic to humans. The

coordinates of Table 1 may be used to find the orientation of the unknown molecule in the crystal, and electron density maps calculated. These maps can then be interpreted with the sequence of the species in question, and the coordinates of the 30S structure described herein can be used to help and speed interpretation. In this way, the structure of the 30S subunit crystal of the invention facilitates the determination of structures of 30S subunits and whole ribosomes from other organisms. (emphasis added)”

In view of the high degree of conservation of ribosome structure known as of the filing date of the application, as disclosed in the afore-mentioned references and in the instant application, one of skill in the art would accept that there is also conservation between the crystal structure of the 30S ribosomal subunit between prokaryotic species. In view of the above, Applicants submit that claims 1-4 and 12-13 are properly enabled for a crystal structure of a prokaryotic 30S ribosomal subunit derived from *Thermus thermophilus*, as well as from other species that have conservation in ribosomal structures.

Claims 1-4 and 12-13, have been amended to recite “A crystal of a prokaryotic 30S ribosomal subunit...” Withdrawn claims 5-11 have been similarly amended.

Claims 1-4 and 13, have been amended to replace the term “having” with the phrase “consisting of”. Withdrawn claims 5-11 have been similarly amended.

In view of the above amendments, Applicants assert that claims 1-4 and 12-13 are properly enabled.

The Office Action also asserts that “the specification is not enabled for those crystals beyond those, which consist of a structure as defined by the coordinates of Tables 1-4 ”. Applicant notes that with regard to the elected species of paromomycin, a structure as defined by the coordinates of Table 1 is recited in Claims 1-4, 7 and 13. Therefore, Applicant contends that claims 1-4, 7 and 12-13 are enabled.

Applicant further notes that with regard to the nonelected species of Streptomycin and Spectinomycin, a structure as defined by the coordinates of Table 1 is recited in Claims 1, 5-6

and 13 for Streptomycin, and in Claims 1, 8 and 13, for Spectinomycin. Therefore, Applicant contends that claims 1, 5-6, 8 and 12-13 are enabled

Further with regard to the nonelected species of Tetracycline, a structure as defined by the coordinates of Table 2, is recited in Claims 1, 9, and 13 so Applicants contend that claims 1, 9 and 12-13 are enabled.

Further with regard to the nonelected species of pactamycin, a structure as defined by the coordinates of Table 3, is recited in Claims 1, 10 and 13, so Applicants contend that claims 1, 10 and 12-13 are enabled.

Further with regard to the nonelected species of hygromycin B, a structure as defined by the coordinates of Table 4, is recited in Claims 1, 11 and 13, so Applicants contend that claims 1 and 11-13 are enabled.

Further, the instant specification discloses in the third paragraph of the “Summary of the Invention” Section, the crystal product with the limitations recited in the instant claims, and discloses in the Materials and Methods Section how to make the crystal. Further, the instant specification also discloses how to use the structure information gained from the recited crystal products in the paragraphs located under the heading entitled “Functional Insight from the Structure of the 30S Ribosomal Subunit”.

### ***Written Description***

Claim 12 is rejected under 35 U.S.C. 112, first paragraph, for lack of Written Description. The Office Action asserts that while Applicants disclose the crystal structure of the *thermus thermophilus* 30S subunit having a resolution of 3.05 Å, Applicant’s disclosure does not provide written support for any 30S subunit having a resolution less than 3 Å. Applicants note that the last paragraph of page 4 and the first paragraph of page 5 discloses a crystal structure of the 30S ribosomal subunit and specifically discloses in line 2 of page 5 that “An advantageous feature of these structures are that they diffract beyond 3 Å resolution”. Therefore, Applicants contend that Applicants’ disclosure does indeed provide written support for “A crystal of a 30S subunit bound to the antibiotic selected from the group of paromomycin, streptomycin, spectinomycin,

tetracycline, pactamycin and hygromycin B, having a resolution numerically less than about 3 Å” as recited in claim 12. Accordingly, Applicant requests reconsideration and withdrawal of the written description rejection.

### ***Claim Rejections-35 USC § 102***

Claim 12 is rejected under 35 U.S.C. 102(b), as being clearly anticipated by Clemons et al (1999).

Applicants submit that for a determination of anticipation to be proper, the prior art reference must disclose each and every limitation of the claim. *Atlas Powder Company et al. v. IRECO, Incorporated et al.*, 190 F.3d 1342, 1347 (Fed. Cir. 1999).

The Office Action states that Clemons et al. teaches the crystal structure of a bacterial 30S ribosomal subunit at 5.5 Å is better than 3 Å. The Office Action asserts that Clemons et al. anticipates the limitation of “better” recited in Claim 3. However, Applicants note that claim 3 as amended, does not recite the term “better”. Because claims 3 does not recite the term “better” and because Clemons et al does not teach a 30S ribosomal subunit having a resolution numerically less than about 3 Å, as recited in amended claim 12, Applicants contend that the Clemons et al. reference does not anticipate newly amended Claim 12. Accordingly, Applicants request reconsideration and withdrawal of the rejection.

### ***Double Patenting***

Claims 1-4, 12 and 13 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4 of copending Application No. 09/904,779 in view of Ramakrishnan et al.

In response to this rejection, Applicants submit that they will submit a terminal disclaimer to disclaim any portion of a patent issuing from the present application which would extend beyond the term of a patent issuing from the 09/904,779 application, upon notification of allowable claims in the present application.



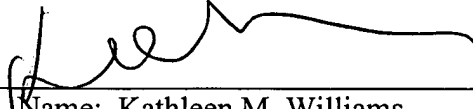
*Conclusion*

Applicant submits that all claims are allowable as written and respectfully request early favorable action by the Examiner. If the Examiner believes that a telephone conversation with Applicant's attorney/agent would expedite prosecution of this application, the Examiner is cordially invited to call the undersigned attorney/agent of record.

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